

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY


(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 19 SEP 2005

WIPO

PCT

Applicant's or agent's file reference PC20548A		<b>FOR FURTHER ACTION</b>		See Form PCT/PEA/416
International application No. PCT/IB2004/001120		International filing date (day/month/year) 31.03.2004	Priority date (day/month/year) 14.04.2003	
International Patent Classification (IPC) or national classification and IPC C07D207/327, C07D405/06				
Applicant WARNER-LAMBERT COMPANY LLC et al.				
<p>1. This report is the International preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 6 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 9 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>				
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Certain defects in the international application</p> <p><input type="checkbox"/> Box No. V Certain observations on the international application</p> <p><input type="checkbox"/> Box No. VI Certain observations on the international application</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>				
Date of submission of the demand  21.05.2004		Date of completion of this report  02.08.2005		
Name and mailing address of the international preliminary examining authority:   European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840		Authorized Officer  Hoepfner, W  Telephone No. +49 30 25901-337		



**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/B2004/001120

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**Box No. I Basis of the report**

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1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
  - ☐ publication of the international application (under Rule 12.4)
  - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements\*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

**Description, Pages**

1-36 as originally filed

**Claims, Numbers**

1-11 received on 09.05.2005 with letter of 02.05.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
  - ☐ the claims, Nos.
  - ☐ the drawings, sheets/figs
  - ☐ the sequence listing (*specify*):
  - ☐ any table(s) related to sequence listing (*specify*):

\* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY**

International application No.  
PCT/IB2004/001120

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**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

**2. Citations and explanations (Rule 70.7):**

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement**

- D1: US-B1-6 476 235 (NELSON JADE DOUGLAS ET AL) 5 November 2002 (2002-11-05)
- D2: E. FALOMIR ET AL.: "Stereoselective synthesis of spicigerolide"  
TETRAHEDRON LETTERS, vol. 44, 13 January 2003 (2003-01-13), pages  
539-541, XP002294837 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM.  
NL
- D3: P. B. GREER ET AL.: "Synthetic studies directed toward the phorboxazoles:  
preparation of the C3-C15 bisoxane segment and two stereoisomers"  
TETRAHEDRON, vol. 58, 22 June 2002 (2002-06-22), pages 6009-6018,  
XP002294838 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM. NL

**Allowability of amendments**

The present claims 1-11 are based on either original claims 1-5 and 7-11 or the description (pages 4, 7, 14, 20, 25).

Hence, the present claims are allowable under Art. 34(2)(b) PCT.

**Novelty**

The document D1 discloses a similar process for the preparation of compound (I) of present claim 1 (see column 1, lines 13-33; columns 43, 44, formulae; claim 1, formulae 8, 12, 13). The processes of claims 1, 6 and 7 differ from the process of D1 in the use of intermediate IV.

The documents D2 and D3 disclose analogous processes for the sequence II → (III, VII) → IV → V according to present claims 1 and 6. However, D2 and D3 are silent on the use of there respective processes in a process for the preparation of target compound (I) (see **D2**: page 540, Scheme 3; **D3**: page 6010, Figure 1; page 6011, Schemes 4, 5).

None of these documents refers to compounds of present claim 11 or processes for their preparation.

In view of this prior art, novelty has to be acknowledged for the subject-matter of present

**INTERNATIONAL PRELIMINARY  
REPORT ON PATENTABILITY  
(SEPARATE SHEET)**

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independent claims 1, 6 and 7-11 and the present dependent claims 2-5.

**Inventive step**

Document D1, which is in fact assigned to the assignee of the present application, is deemed the closest prior art for the novel subject-matter, since it addresses the same problem, namely provision of a process for the production of an intermediate of formula (I) suitable for the preparation of atorvastatin calcium.

The distinguishing feature between the novel subject-matter and D1 is the metathesis step IV → V.

In the absence of any evidence for an unexpected technical effect linked to this feature, the objective problem underlying the novel subject-matter can merely be regarded as the provision of a further process for the production of an intermediate of formula (I) suitable for the preparation of atorvastatin calcium.

The presently claimed solution to this very general problem was the modification of the D1 process by applying the metathesis reaction of D2 or D3 to the D1 process.

However, since this particular combination of reaction steps taken from different sources was not derivable from the prior art on file either read alone or in combination, the presence of inventive step has to be acknowledged for the novel subject-matter, even in the absence of a technical effect.

**Industrial applicability**

There is no doubt that the subject-matter of the present claims on file is industrially applicable.

**Re Item VIII**

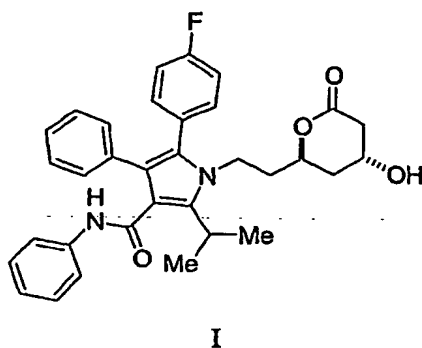
**Certain observations on the International Application**

An independent claim shall contain all essential features necessary to perform the invention without undue burden of experimentation.

With this lack of enabling disclosure, present claims 8 and 9 are rendered unclear due to the use of the term "chiral auxiliary".

## CLAIMS


1. A process for preparing a compound of formula (I)

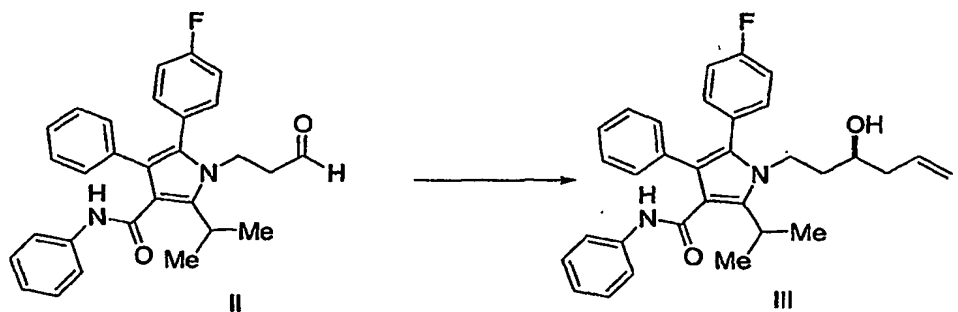


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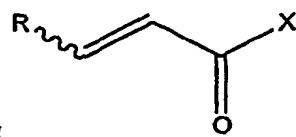
comprising:

- (a) contacting in a solvent optionally in the presence of a chiral Lewis acid a

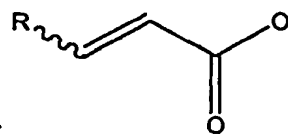
compound of formula (II) with , wherein M is SiCl<sub>3</sub>, SiMe<sub>3</sub>, B(OH)<sub>2</sub>, CuLi, MgBr, ZnBr, InBr, SnR<sub>3</sub> wherein R<sub>3</sub> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, to give a compound of formula (III):



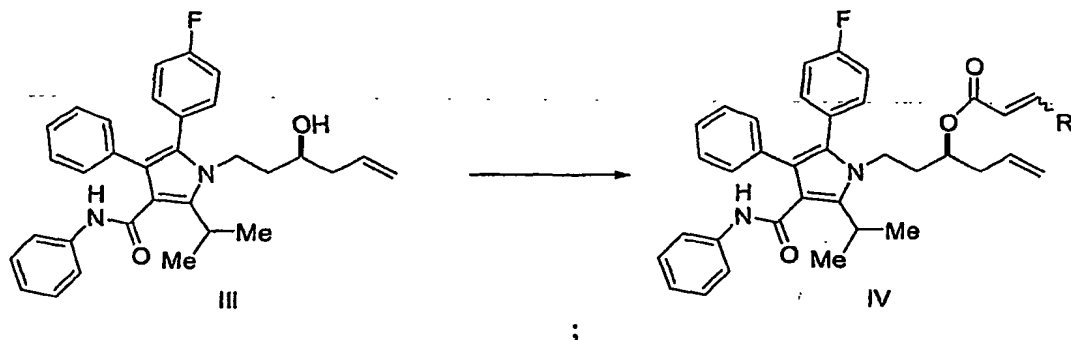
- (b) conversion of the compound of formula (III) to an acryloyl ester of



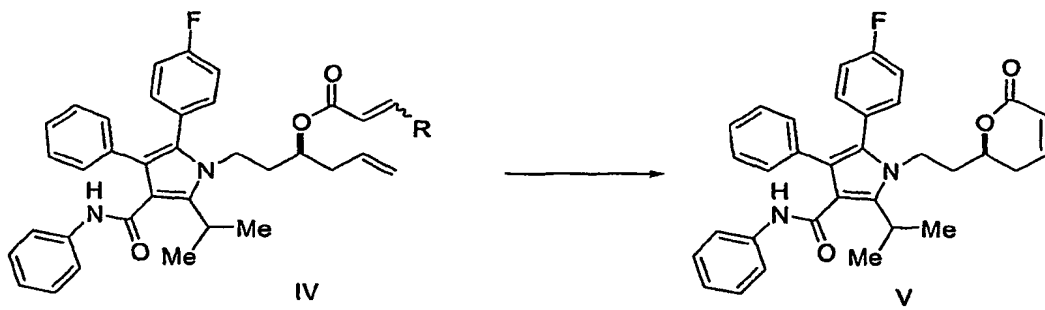
formula (IV) in the presence of base using



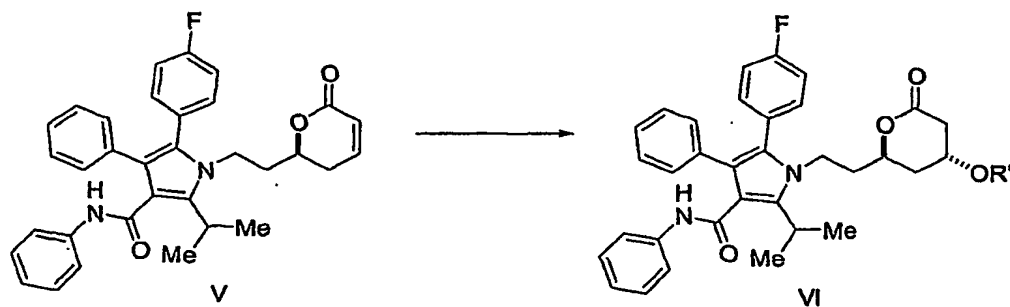
wherein X is Cl, Br, I, or  $\text{C}_6\text{H}_4$ , and R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or phenyl, or an acryloyl activated ester equivalent:



(c) contacting in a solvent the acryloyl ester (IV) with a catalyst to afford 5,6 dihydro pyran-2-one V:



(d) converting the compound of formula (V) to a compound of formula (VI) via facial selective 1,4 addition of allyl or benzyl alcohol:

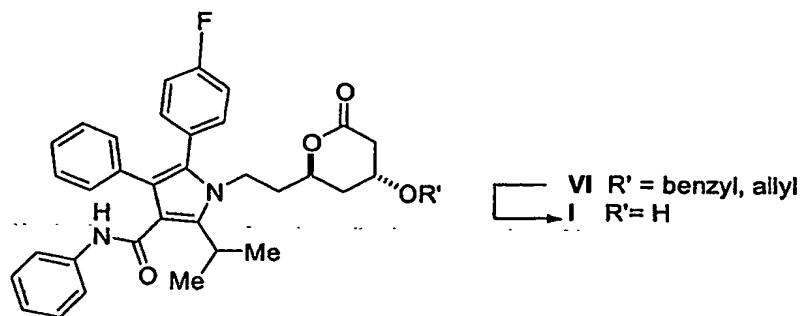



R' = benzyl, allyl



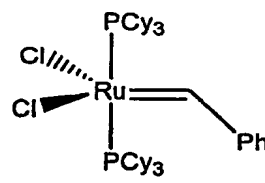
and

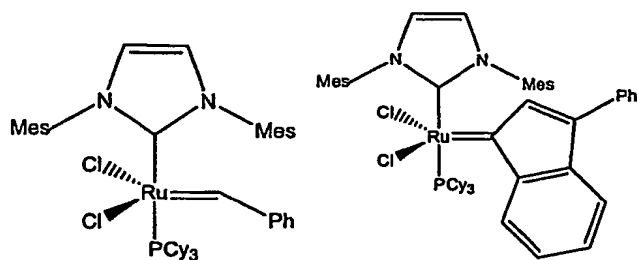
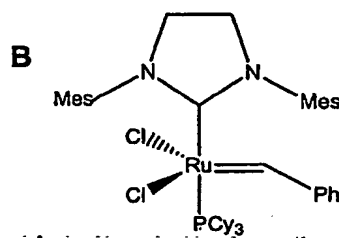
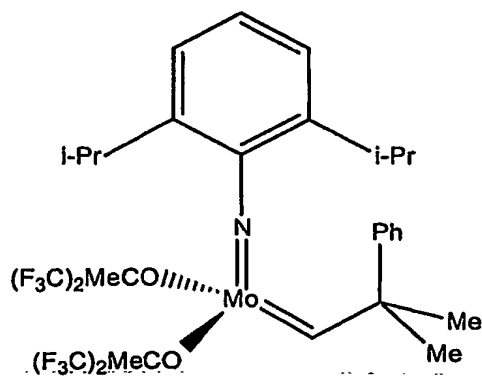
- (e) removal of the allyl or benzyl moiety in the compound of formula (VI) via hydrogenolysis to give a compound of formula I:



2. The process of step (a) of claim 1, wherein  is allyl tri-*n*-butylstannane, allyl trimethylsilane, allyl trichlorosilane, allyl magnesium bromide, or allyl zinc bromide, optionally used in the presence of an amino alcohol or diamine or a Lewis Base.
3. The process of step (a) of claim 1 carried out in the presence of a chiral Lewis acid, optionally generated in situ from boron tribromide and (S,S)-1,2-diamino-1,2-diphenylethane *bis*-toluenesulfonamide.
4. The process of step (b) of claim 1 wherein the base is an amine base selected from the group consisting of triethyl amine, N,N dimethyl amino pyridine, DBU, and DBN optionally in the presence of a catalytic amount of DMAP and the polar nonprotic solvent is dichloromethane.

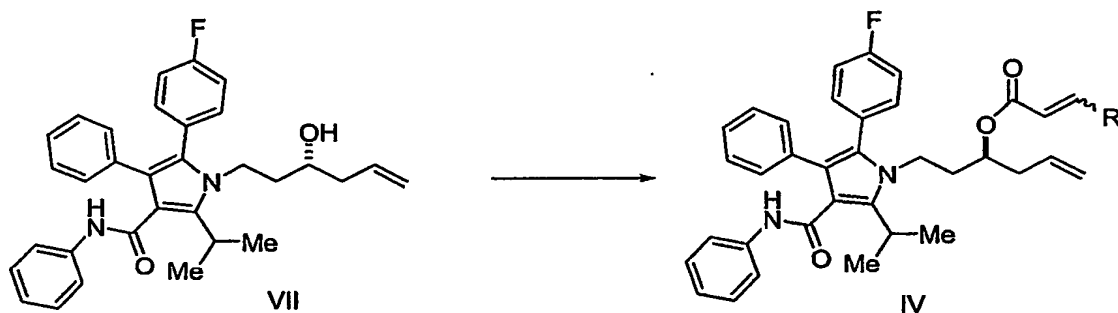
5. The process of step (c) of claim 1, wherein the catalyst is






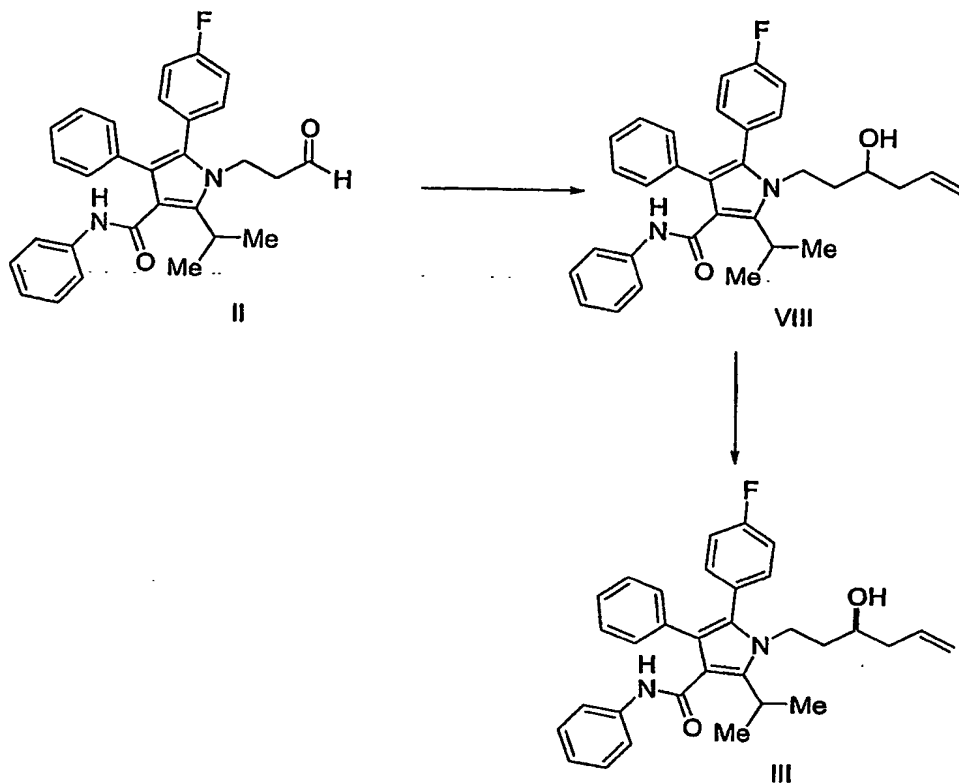
, or benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene] dichloro (tricyclohexylphosphine)ruthenium.

6. A process for preparing the compound of formula IV, comprising converting a compound of formula VII via displacement reaction:

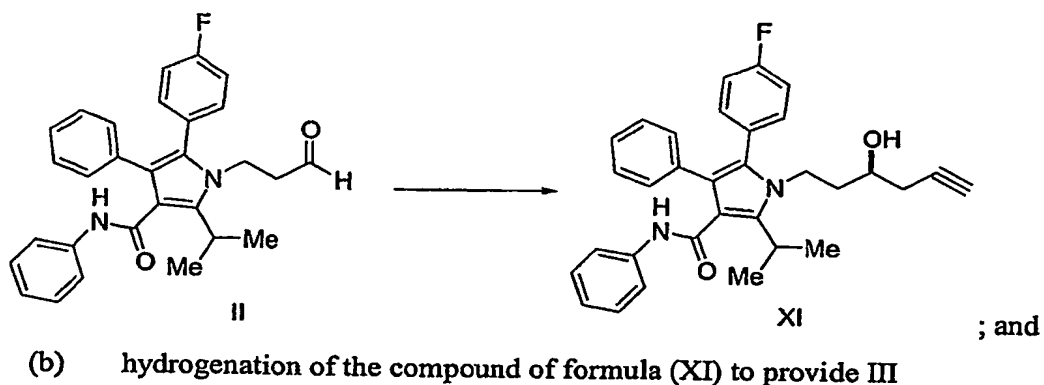


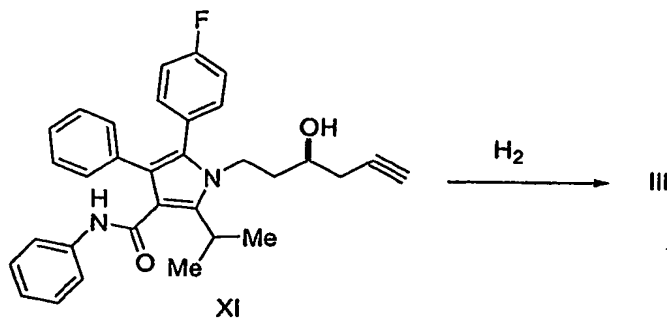
7. A process for preparing a compound of formula III comprising
- (a) contacting in a solvent optionally in the presence of a nonchiral Lewis acid a compound of formula (II) with , wherein M is SiCl<sub>3</sub>, SiMe<sub>3</sub>, B(OH)<sub>2</sub>, CuLi, MgBr, ZnBr, InBr, SnR<sub>3</sub> wherein R<sub>3</sub> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, to give a

compound of formula VIII, followed by isolation of the compound of formula III via chromatographic separation or resolution:



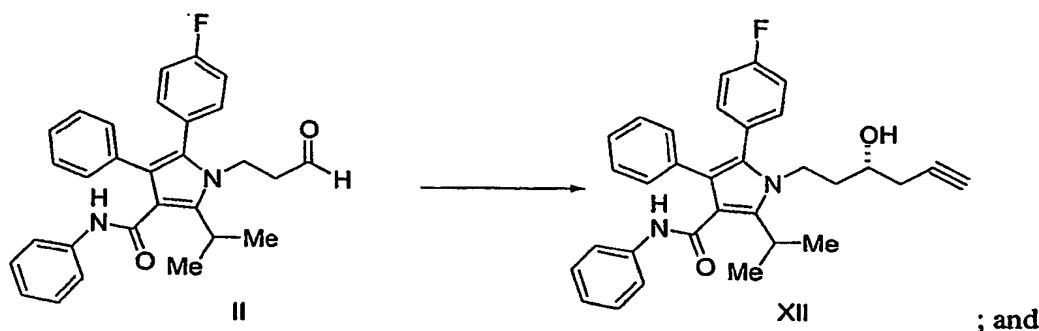
8. A process for preparing a compound of formula III as recited in claim 1, comprising:
- contacting (II) with an allenylboronic ester in the presence of a chiral auxiliary to give a compound of formula (XI):



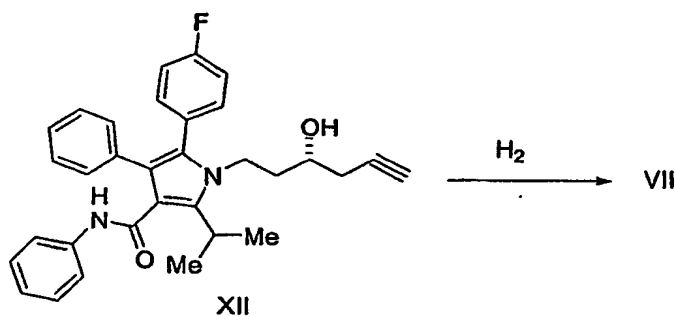


9. A process for preparing the compound of formula VII as recited in claim 6, comprising:

- (a) contacting (II) with an allenylboronic ester in the presence of a chiral auxiliary to give a compound of formula (XII):

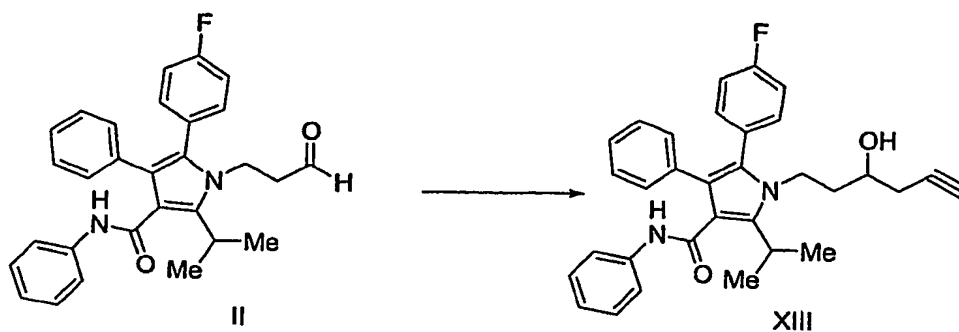


- (b) hydrogenation of the compound of formula (XII) to provide VII



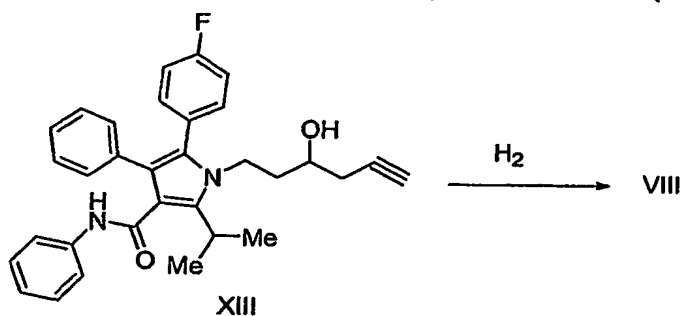
10. A process for preparing a compound of formula VIII as recited in claim 7, comprising:

- (a) contacting (II) with allenylboronic acid or an allenylboronic ester to give a compound of formula (XIII):

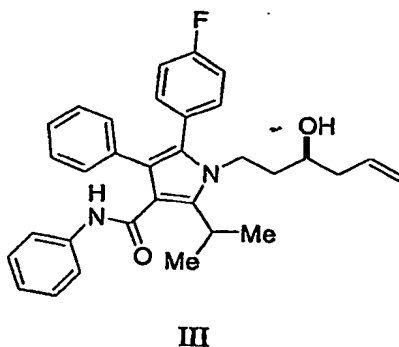


; and

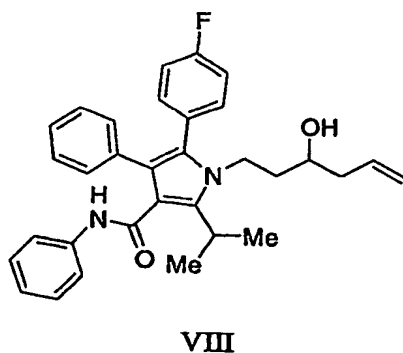
(b) hydrogenation of the compound of formula (XIII) to provide VIII



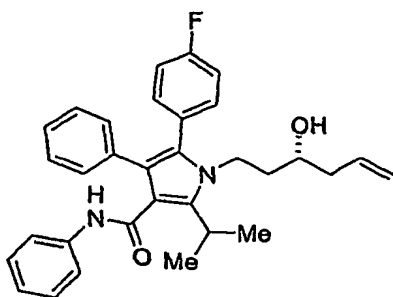
11. Compounds of the following formulae:



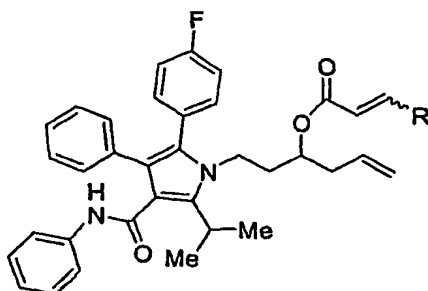
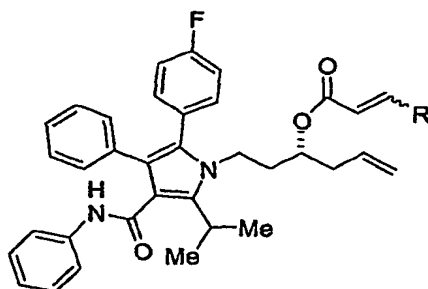
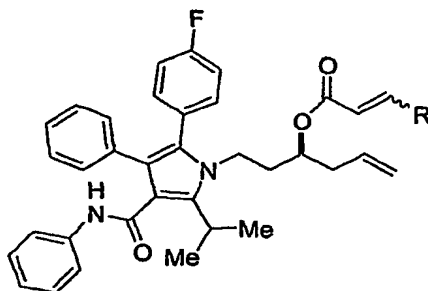
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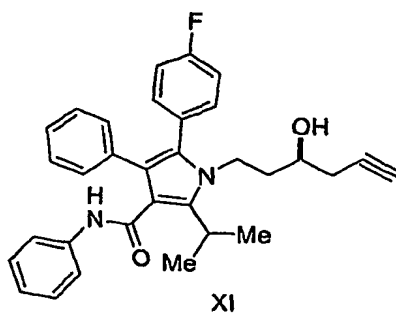


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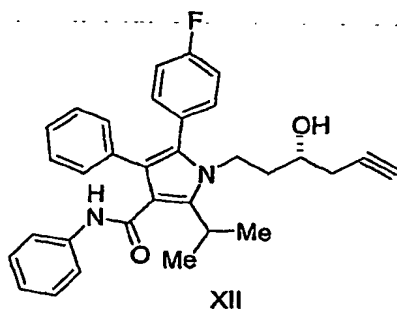
VII

IX, wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or phenyl;X, wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or phenyl;IV, wherein R is H, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or phenyl;



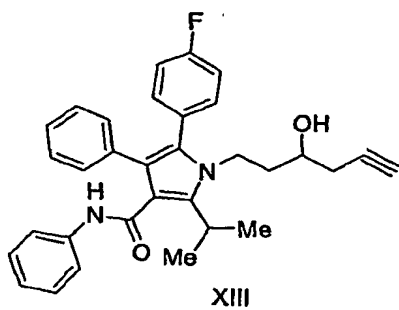
XI

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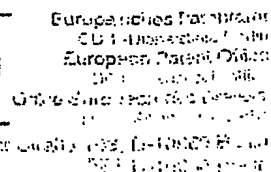


XII

; and



XIII



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[illegible]

1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100. 101. 102. 103. 104. 105. 106. 107. 108. 109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 120. 121. 122. 123. 124. 125. 126. 127. 128. 129. 130. 131. 132. 133. 134. 135. 136. 137. 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155. 156. 157. 158. 159. 160. 161. 162. 163. 164. 165. 166. 167. 168. 169. 170. 171. 172. 173. 174. 175. 176. 177. 178. 179. 180. 181. 182. 183. 184. 185. 186. 187. 188. 189. 190. 191. 192. 193. 194. 195. 196. 197. 198. 199. 200. 201. 202. 203. 204. 205. 206. 207. 208. 209. 210. 211. 212. 213. 214. 215. 216. 217. 218. 219. 220. 221. 222. 223. 224. 225. 226. 227. 228. 229. 230. 231. 232. 233. 234. 235. 236. 237. 238. 239. 240. 241. 242. 243. 244. 245. 246. 247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259. 260. 261. 262. 263. 264. 265. 266. 267. 268. 269. 270. 271. 272. 273. 274. 275. 276. 277. 278. 279. 280. 281. 282. 283. 284. 285. 286. 287. 288. 289. 290. 291. 292. 293. 294. 295. 296. 297. 298. 299. 300. 301. 302. 303. 304. 305. 306. 307. 308. 309. 310. 311. 312. 313. 314. 315. 316. 317. 318. 319. 320. 321. 322. 323. 324. 325. 326. 327. 328. 329. 330. 331. 332. 333. 334. 335. 336. 337. 338. 339. 340. 341. 342. 343. 344. 345. 346. 347. 348. 349. 350. 351. 352. 353. 354. 355. 356. 357. 358. 359. 360. 361. 362. 363. 364. 365. 366. 367. 368. 369. 370. 371. 372. 373. 374. 375. 376. 377. 378. 379. 380. 381. 382. 383. 384. 385. 386. 387. 388. 389. 390. 391. 392. 393. 394. 395. 396. 397. 398. 399. 400. 401. 402. 403. 404. 405. 406. 407. 408. 409. 410. 411. 412. 413. 414. 415. 416. 417. 418. 419. 420. 421. 422. 423. 424. 425. 426. 427. 428. 429. 430. 431. 432. 433. 434. 435. 436. 437. 438. 439. 440. 441. 442. 443. 444. 445. 446. 447. 448. 449. 450. 451. 452. 453. 454. 455. 456. 457. 458. 459. 460. 461. 462. 463. 464. 465. 466. 467. 468. 469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481. 482. 483. 484. 485. 486. 487. 488. 489. 490. 491. 492. 493. 494. 495. 496. 497. 498. 499. 500. 501. 502. 503. 504. 505. 506. 507. 508. 509. 510. 511. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 522. 523. 524. 525. 526. 527. 528. 529. 530. 531. 532. 533. 534. 535. 536. 537. 538. 539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560. 561. 562. 563. 564. 565. 566. 567. 568. 569. 570. 571. 572. 573. 574. 575. 576. 577. 578. 579. 580. 581. 582. 583. 584. 585. 586. 587. 588. 589. 590. 591. 592. 593. 594. 595. 596. 597. 598. 599. 600. 601. 602. 603. 604. 605. 606. 607. 608. 609. 610. 611. 612. 613. 614. 615. 616. 617. 618. 619. 620. 621. 622. 623. 624. 625. 626. 627. 628. 629. 630. 631. 632. 633. 634. 635. 636. 637. 638. 639. 640. 641. 642. 643. 644. 645. 646. 647. 648. 649. 650. 651. 652. 653. 654. 655. 656. 657. 658. 659. 660. 661. 662. 663. 664. 665. 666. 667. 668. 669. 670. 671. 672. 673. 674. 675. 676. 677. 678. 679. 680. 681. 682. 683. 684. 685. 686. 687. 688. 689. 690. 691. 692. 693. 694. 695. 696. 697. 698. 699. 700. 701. 702. 703. 704. 705. 706. 707. 708. 709. 710. 711. 712. 713. 714. 715. 716. 717. 718. 719. 720. 721. 722. 723. 724. 725. 726. 727. 728. 729. 730. 731. 732. 733. 734. 735. 736. 737. 738. 739. 740. 741. 742. 743. 744. 745. 746. 747. 748. 749. 750. 751. 752. 753. 754. 755. 756. 757. 758. 759. 760. 761. 762. 763. 764. 765. 766. 767. 768. 769. 770. 771. 772. 773. 774. 775. 776. 777. 778. 779. 780. 781. 782. 783. 784. 785. 786. 787. 788. 789. 790. 791. 792. 793. 794. 795. 796. 797. 798. 799. 800. 801. 802. 803. 804. 805. 806. 807. 808. 809. 810. 811. 812. 813. 814. 815. 816. 817. 818. 819. 820. 821. 822. 823. 824. 825. 826. 827. 828. 829. 830. 831. 832. 833. 834. 835. 836. 837. 838. 839. 840.

International application No: PCT/B2004/001120

# LUFTPOST PRIORITAIRE

## Briefe zum Kilotariff

SECURITY CLEARED  
04 AOUT 2005  
CONTROLE de SECURITE